REMARKS

The following claims are currently being amended or cancelled:

(A) Pending claims 1, 6, 12, 13,, 18, 24, 27, 33-36 are amended.

(B) Withdrawn claims 66-68 and 72 are amended.

(C) Claims 4 and 23 are hereby cancelled without prejudice or disclaimer.

New claims 73-78 are added.

All the new amendments are and new claims are supported by the original claims and the specification throughout. A number of the amendments simply change dependency due to cancellation of claims 4 and 23. The amendments to claims 12 and 27 are supported by Figure 2 of the application. Compare the CB4-P and CB4-P/ova10 sequences (the latter comprising the heterologous sequence), and note that amino acids/codons 130-135 (aa's S-T-A-T-N-S) were deleted.

The amendments to claims 33-37 (and withdrawn claims 66 and 68) correspond to claim language suggested by the Examiner on January 12, 2005, as part of a series of interviews and discussions over the period of almost a week. The amendments to claims 67 results from the comments of the Examiner during those same discussions. The language of new claim 73 also reflects language proposed by the Examiner at that time.

The unelected, withdrawn claim 72 is being amended to remove language inadvertently left after the previous amendment of that claim. The other withdrawn claims are amended to remain commensurate in scope with the elected product claims for later rejoinder.

New claims 74-78 re-introduce language that Applicants had deleted earlier in response to objections and an incomplete analysis by the Office. This is discussed more in Section I, below

No new matter is added by these amendments. Entry and allowance of the amended claims is respectfully requested.

I. Reopening of Prosecution and Discussion of Prior Activity

Applicants acknowledge the Office's re-opening of prosecution in view of "further considerations:" and the Examiner's statement of regret regarding the inconvenience to Applicant. Applicants cannot let that latter comment pass without stating that the history of the examination in this case, in part due to the changing of Examiner's after extensive prosecution have indeed been a major inconvenience truly worked an economic hardship on the Applicants. Applicants believe they have been subject to an unusual amount of "back-and-forth-changing-of-the-mind" though obviously, they do not blame any individual at the Office, each of whom is just "doing his/her job."

Applicants and the undersigned thank Examiner Chen (and SPE Housel in the background) for their attention and efforts during intense series of telephonic interviews and email exchanges during the week of 12 January 2005, when attempts were made by both sides to reach agreement on claim language. Unfortunately, no agreement was reached at that time, leading to the current Office Action.

Prior to this Response, claims 1, 3,4,6-15, 17-18,20-28 and 30-36 were under examination. Claims 2, 19 and 54-72 stand withdrawn. At this time, claims 4 and 23 are being cancelled, and claims 73-76 are added, so the pending claims are 1, 3, 6-15, 17-18, 20-22, 24-28, 30-36 and 73-76.

Applicants acknowledge the Office's removal of the rejection of claims 1, 3,4,6-15, 17-18, 20-28 and 30-36 under 35 U.S.C.§ 112, first paragraph, due to "new matter" as being moot in view of the prior amendment which deleted the objected-to language ("non-coxsackievirus"). The Office acknowledged that the Applicant has presented arguments relating to the rejection, but those arguments were not addressed by the Examiner in view of the deletion of that language. The Office Action states that, should Applicant amend the claims to recite the originally "objected to" phrase, this issue will be addressed, presumably fully, as it had not been when the original rejection was made (in the paper mailed June 3, 2004). Applicants are adding a very short set of new claims which re-introduce the "non-coxsackievirus" language (as new claims 74-78) and look forward to either allowance of these claims or a full legal analysis as to why they are not patentable.

II. NEW REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. First New Rejection

Claims 3, 4, 6-15, 17, 20-28 and 38-36 are rejected as failing to comply with the written description requirement. The Office asserts that the claims include subject matter that was not adequately described in the specification to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> The Office asserts that "it is apparent that coxsackievirus CB4-P is required to practice the claimed invention because they are a necessary limitation for the success of the invention as stated in the claims."

The Office reminds applicants that if this "required element" is not "known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public" the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of coxsackievirus CB4-P.

> It is the Office's view that
>
> one cannot practice the claimed invention without the *specifically named CB4-P coxsackievirus strain*. Therefore, access to coxsackievirus CB4-P is required to practice the invention. While the specification provides a method for obtaining a virus that is like CB4-P, the specification does not provide a repeatable method for obtaining ***the*** CB4-P without access to ***the*** CB4-P and it does not appear to be readily available material. Deposit of coxsackievirus CB4-P in a recognized deposit facility would satisfy the enablement requirements of 35 U.S.C. 112., because the strains would be readily available to the public to practice the invention claimed

B. Applicants' Response to First New Rejection

Applicants respectfully direct the Office's attention to the Ramsingh-3 Declaration which goes through some history of the CB4 virus that ended up being called, variously, the JVB strain or the CB4-P virus.

As stated in the Declaration CB4-P was a mere designation of convenience given to the JVB virus after it was handed over to Dr. Ramsingh (see Sec. 4). Dr. Ramsingh indicates at several points thereafter that CB4-P and JVB are, for all intents and purposes, the same virus (99.8% identical at the nucleotide level and 99.6% at the amino acid level).

The specification makes clear that CB4-P was used as "prototype" in the making of a broader invention directed to an engineered attenuated coxsackievirus B4 virion that stably expresses a

heterologous protein in a host. See page 13, lines 16-19. At page 13, line 35, - page 14, line 15, the specification reads

> The findings made with the CB4-P virus apply to any attenuated B4 coxsackievirus. Thus all embodiments of the present invention described herein, are intended to equivalently apply to viral vectors made from any attenuated B4 coxsackievirus...The prototype virus CB4-P is originally derived from JVB and is highly similar to JVB in nucleotide and amino acid sequence. Because of this strong conservation, the JVB virus is expected to perform as an equivalent to CB4-P in the generation and use of the viral vector described herein.

The above having been said, Applicants wish to emphasize Sections 7 and 8 of the Ramsingh-3 Declaration which explain why a skilled artisan would be fully enabled to practice the presently claimed invention without undue experimentation, and certainly without any further inventive effort. CB4-P viruses, such as JBV, deposited at the ATCC are publicly available. Moreover, CB4 viruses can be isolated from "the wild" (i.e., an infected subject), grown in culture and readily analyzed and sequences. That, along with information in the present application and other sources of the publicly available sequence information, including that in Jenkins *et al.* [2], *supra*; Ramsingh *et al.*, 1992[3], the GenBank and Caggana *et al.*, 1993 (cited by the Office in a pending art rejection; see below), would enable one to make, verify and use the genetically engineered virions (or nucleic acid molecules) of the present claims without undue experimentation. A skilled artisan can

> ...start with any CB4 virus that is described in the application or known in the field, and *if desired*, can modify the viral nucleic acid sequence to make it match up perfectly with the CB4-P virus ... described in the application ... However ...there is no reason the starting virus would have to match up perfectly over its entire genome. It just needs to have the correct sequences at the sites used to introduce the heterologous nucleic acid, and that is described in detail in the specification...

Ramsingh-3 Declaration, Sec. 7. Indeed, the present specification says (at page 14, lines 23) that:

> Through sequence alignment, one of skill in the art can identify nucleotide and amino acid sequences of other CB4 viruses (e.g., JVB) which correspond to the nucleotides or amino acids of CB4-P. Such a determination falls within the definition of routine experimentation.

This fact is supported by statements in the Ramsingh-3 Declaration and, independently, in the Tracy Declaration.

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[2] Jenkins *et al.* 1987. "The complete nucleotide sequence of coxsackievirus B4 and its comparison to other members of the picornaviridae." *J. Gen. Virol. 68*:1835-1848) - copy attached

[3] Ramsingh *et al.* 1992. "Identification of candidate sequences that determine virulence in Coxsackievirus B4." *Virus Res 23*:281-292 (copy attached)

In his Declaration (see in particular Sec. 9), Dr. Steven Tracy, an expert in the coxsackievirus field[4], maintains that a skilled person could practice the claimed invention without the need to resort to any deposit of CB4-P. It is therefore clearly evident to one skilled in the art that the Applicants were "in possession" of the claimed invention. Moreover, Dr. Tracy emphasizes how the teachings of the application would enable its practice with any virus that is genetically *equivalent* to CB4-P to produce the chimeric recombinant virions as presently claimed.

> Once a person skilled in the field has been apprised of the present invention and read the application, that person will be able to practice it as written in the claims. Indeed, what works in CB4-P to create a virus expressing a heterologous polypeptide that can act a as an immunogen would also work in CB4-JVB or CB4-V...

Tracy Declaration, Sec. 9. The Ramsingh-3 Declaration also makes a similar assertion (in Secs. 6-8) that any virus that is a genetic equivalent of CB4-P could readily be used to practice the claimed invention because

> ...genetically equivalent viruses can be easily manipulated by those skilled in this field, as described in the specification, to allow insertions of heterologous nucleic acids. The deposited JVB strain of CB4 (ATCC # VR-184) is genetically equivalent to CB4-P. Any CB4 virus, including the deposited JVB strain, can be used to practice the claimed invention.

(Ramsingh-3 Declaration at Sec. 8). Tracy takes an even more expansive view with respect to what the application enables - namely, practice of the present invention by inserting heterologous sequences (encoding peptide products to be used as immunogenic viral vectors) into the P1 region of other coxsackievirus B serotypes (CB1, CB2, CB3, CB5 and C6).

In view of the foregoing remarks and statements made by two independent expert declarants, it is believed that this ground for rejection under § 112, first paragraph may properly be withdrawn.

C. Second New Rejection

Claims 1, 3, 18 and 20-22 were rejected due to lack of enablement. The Office asserts that the specification, while being enabling for a recombinant attenuated coxsackievirus B4 virion (or nucleic acid encoding said virion) which is engineered to contain a heterologous nucleic acid inserted within the P1 region of its genome, does not enable an insertion within any region of the open reading frame ("ORF") of the genome.

[4] and even a co-inventor of a prior art reference that had been cited earlier in this case, but which had been overcome)

D. Applicants' Response to Second New Rejection

Applicants apologize if they are the source of confusion that prompted this rejection. Claim 1, by requiring that the inserted polypeptide be fused to a capsid protein, in effect requires that the heterologous nucleic acid be inserted in the P1 region, because the P1 region is the only region that encodes (all) the viral capsid proteins (VP1-VP4). Thus, although worded differently, claims 1 and 4 are of the same scope with respect to the location of the heterologous nucleic acid insert. Claims 3 and 4 are of identical scope. The same is true for claims 18, and 20-22 vs claim 23. Claims 18 and 20 are of the same scope with respect to the location of the insert, and claim 20 and 23 are of identical scope. The Examiner clearly picked up on this issue in the subsequent part of her remarks describing the rejection (emphasis added):

> The claims encompasses a recombinant virion (or nucleic acid) wherein a heterologous nucleic acid is inserted within any part ***{this is the point of confusion, as it is not "any part"}*** of the ORF of its genome. The nature of the invention is the insertion of heterologous nucleic acid encoding a polypeptide into a CB4 genome to produce a fusion protein. The P1 region of the ORF contains *all the structural proteins*, whereas the P2 and P3 regions contain the *non-structural proteins* (specification, page **3**, lines 19-23). In order for the heterologous nucleic acid to be expressed as a fusion protein with the capsid protein of the virion, the insertion would have to take place in the capsid region, namely, the P1 region (specification, page 6, lines 12-15). The state of the art[5] shows that a coxsackievirus B4P (CB4-P) virion expressed a human immunodeficiency virus (HIV) p24 *gag* protein when inserted into the VP 1 region of the CB4-P ORF (Halim et *al., AIDS Res. Hum. Retrovir*, 2000, *16*: 1551- 1558 (pg 1551, col 2, full para)...
>
> Given the breadth of the claims, the state of the art, the level of skill ..., the claims are only enabled for insertion in the P1 region in order to result in a fusion with the ***{"the" should read "a"}*** capsid protein of CB4.

Thus, claim 1, even in its present form, is in fact enabled for the same reason that claim 4 is enabled. (Claim 18 is enabled for the same reason that claim 23 is enabled). All these claims are directed either to a recombinant attenuated coxsackievirus B4 virion (or to its constituent nucleic acid genome) which is engineered to contain a heterologous nucleic acid inserted within the **P1 region - not just "any region" -** of the ORF. Applicants have elected to amend claim 1 to include the language of claim 4 (and claim 18 to include the language of claim 23) with respect to the P1 region. Claims 4 and 23 are being canceled as duplicative. This ground for rejection is therefore moot and may be withdrawn.

[5] The disclosure of the cited reference indeed constitutes part of this specification.

III. Rejection under 35 U.S.C. 1 12, Second Paragraph

Claims 13-15 and 28 are rejected as being indefinite. Claims 13-15 include limitations of claim 1, and claim 28 includes limitations of claim 18. The rejected claims recited that the insertion of the nucleic acid is upstream of sequences which encode VP4, and that the encoded heterologous polypeptide is expressed as an amino-terminal fusion of the viral polyprotein and subsequently cleaved off. It is unclear to the Office how the limitations in claims 13- 15 and 28 relate with claims 1 and 18, which require that the encoded polypeptide be expressed as a fusion with a capsid protein which presumably remains fused to the capsid for display to antigen-presenting cells. Clarification and/or correction is required.

Applicants' Response

Again, there appears to be some confusion about the capsid proteins in this rejection. All the products encoded by the P1 region of CB4 are capsid proteins, namely, VP1, VP2, VP3 and VP4. The processing of these proteins includes initially translation as a polyprotein comprising VP0, (which in turn is cleaved to VP4 and VP2) VP1 and VP3. During the processing, as the polyprotein is translated, it undergoes several cleavage steps (by proteases encoded by genes in the P2 and P3 regions of the genome). The Examiner's attention is directed to Figure 1 (Appendix A) which is a schematic intended to illustrate the above process in a "non-recombinant" CB4 virus (Panel A), and two types of recombinant CB4 viruses that comprise a heterologous sequence, as represented by different groups of claims (Panels B and C). Also included in Appendix A for the Examiner's convenience is Figure 2 (which is simply a clearer version of Figure 10 of the application)

Virus A is a "standard" CB4 virus. A P1-encoded polyprotein is produced by translation of nucleic acid, and includes the sequence of a precursor VP0 and two capsid proteins VP3 and VP1. It is represented here as a **VP0-VP3-VP1**. This polyprotein is further processed by proteolytic cleavage into VP0, VP3 and VP1. Upon virion assembly, VP0 is cleaved into VP4 and VP2.

Virus B represents one approach of the present invention ("Strategy 1, claims 7-12; 24-27) in which a heterologous sequence is inserted into the VP1 coding region and encodes an amino acid sequence X which is expressed in the VP1 protein. The latter protein is represented here as **VP1-X-VP1** and the polyprotein is represented as **VP0-VP3-VP1-X-VP1**. As above, the polyprotein is processed into VP0 (which becomes VP4 and VP2), VP3 and **VP1-X-VP1**, which are assembled into the virion capsid. Peptide X appears on the virus as a fusion polypeptide with VP1. (Compare lane C with lanes D and E in the "VP1" region of Fig. 2.) As disclosed in the application,

this configuration is designed to stimulate T helper cell activity upon immunization with these virions.

Virus C represents a second approach of the present invention ("Strategy 2, claims 13-15 and 17; 28-32). In this case, a heterologous sequence is inserted adjacent to the VP4 coding region and encodes a polypeptide sequence Z. This sequence includes a recognition site of known sequence for the viral protease 3C which is expressed in the VP0 precursor. *See, for example, specification at page 9-10, description of Fig. 7* Thus, the polyprotein has the "structure" represented here as **Z-VP0-VP3-VP1**. This is further processed into Z-VP0 and VP3 and VP1 (Compare lane C with lanes D and E in the "V0" region of Fig. 2.). Peptide Z, cleaved from its fusion polypeptide, is transported to the infected cell's endoplasmic reticulum and processed via the MHC class I pathway. Again VP0 (which becomes VP4 and VP2), VP3 and VP1 are assembled into the virion capsid. As disclosed in the application, Peptide Z ends up expressed on cell surfaces and serves to stimulate Cytotoxic T lymphocyte (CTL) activity when a host is immunized with such virions.

Applicants hope the explanation above has clarified the Examiner's understanding of this embodiment of the invention, and explains why claims 13-15 do include the limitations of claim 1 -- because the encoded polypeptide is expressed as a fusion with a capsid protein. However, unlike Strategy 1 (such as in claims 7-12) where the fusion protein indeed "remains fused" to the capsid, in Strategy 2 (claims 13-15), the heterologous sequence is fused to the capsid polyprotein but is designed to undergo proteolytic cleavage at some stage (*i.e.*, does not "**remain fused**" to the capsid protein). Nonetheless, it is expressed on the infected cell surface in association with MHC class I molecules, and **does undergo** "display to antigen-presenting cells." This strategy is employed to stimulate CTL-based immunity (vs. inducing T helper cells and antibodies which is the objective of Strategy 1).

In view of the foregoing, it would be proper to withdraw this ground for rejection.

IV. *Claim Rejections - 35 USC § 102*

Claims l, 3,4, 6-9, 18, 20-26, 31 and 33 are rejected under 35 U.S.C. 102(b) are anticipated by Caggana *et al. (J. Virol.,* 1993,674) - herein after "Caggana".

This reference had previously been applied against the novelty of claims l, 3,4, 18 and 20-26. That rejection was withdrawn in view of the Second Declaration of Dr. Arlene Ramsingh which highlighted the differences between insertion and replacement technology. In view of these

differences, the examiner withdrew that rejection. Upon further consideration, the rejection is reinstated (with regard to claims 1, 3,4, 18 and 20-26, previously rejected) because, in the view of the Office, the claim language is "encompassed by an embodiment disclosed in Caggana."

(a) The Office alleges that the claim language, in its broadest reasonable interpretation, reads on various embodiments of "insertion", stating that insertion can be a deletion/insertion combination. Further, the Office interprets the meaning of "heterologous nucleic acid" in light of the specification, which used the language:

> "The term "heterologous polypeptide" refers to a polypeptide which is not otherwise naturally expressed by the virus. The term "heterologous nucleic acid" refers to any nucleic acid which is not otherwise naturally present in the genome of the virus at the position in which it is inserted."

Based on this, the reference allegedly anticipates claims 1, 3, 4, 6-9, 18, 20-26, 31 and 33.

The Office went through a thorough reasoned restatement of what Applicants are claiming. Caggana was said to teach

> coxsackievirus CB4-P/CB4-V chimeras, in which an attenuated strain, CB4-P expresses heterologous CB4-V proteins of various types (P1, P2, P3) at various regions of the CB4-P genome, including just downstream from codon 129 of VP1, DE loop

(citing to page 4797- 4798, "Construction of recombinant viruses"; page 4798, Figure 1; pages 4799-4801, bridging paragraph; and page 4802, second column, first line).

The VP1 region encodes capsid, which, according to the Office, "itself is immunogenic and thus contains B cell and/or T cell epitopes.

The Office Action discussed Applicants arguments, such as

(1) Caggana's chimerics are not intended to be encompassed by the instant claims because Caggana replaces regions of CB4 viruses with other regions of CB4 viruses. Replacement of CB4-P genes with CV4-V genes is not a heterologous nucleic acid insertion.

The Office acknowledges that the CB4-P and CB4-V strains

> ***[NOTE: in view of the Declarations submitted herewith, the Examiner is asked to take note that it is inaccurate to consider CB4-P and CB4-V as different strains. This and other similar choices of language surely contributed to the overall misinterpretation of this reference in the opinions of the Declarants.]***

of CB4 differ by about 5 amino acids, but then goes on to say that

> they remain structurally distinct strains because they have different amino acid sequences that renders one virulent and the other non-virulent. Even though the virulence is credited to one amino acid residue in the capsid protein of VP1 (Caggana, abstract), the sequences of the two remain different. The VP1 region of CB4-P is not the same as the VP1 region of CB4-V, structurally (amino acid difference) and functionally (virulent, non-virulent).

The Office concludes based on the above that Caggana's chimera meets the claim limitations of being

> a CB4 virion with **heterologous** nucleic acid **inserted** into an open reading frame that results in **fusion** to the capsid protein of the virion, wherein heterologous nucleic acid is defined as 'not otherwise naturally present in the genome of the virus'. In the instant case, the P1 region of **CB4-V** was not naturally present in the genome of the CB4-P virus. Therefore, the claims are encompassed by Caggana.

Applicants' Response to § 102 Rejection

Applicants can do little more here than ask that the Examiner carefully review the Tracy Declaration, the Weiser Declaration and the Vande Woude Declaration. These come from independent sources, none of whom know one another, and who work in varying fields under the broader umbrella of molecular virology and molecular genetics. Applicants will note below some of the salient features of the Declarations - and emphasize the common thread that runs through them. At the outset, it should be said that all of the Declarants are in complete and absolute disagreement with the Office's reading, interpretation and application of Caggana.

A. Heterologous

All of the Declarants (and co-inventor Ramsingh as well in the Ramsingh-3 Declaration) express their expert view that no person in the art would consider the CB4-P and CB4-V viruses nor their nucleic acids and proteins to be "heterologous" to one another. The particular study that was described in Caggana was an example of the exchange of **homologous** sequences between two viruses. As stated by the Declarants, "homologous" is the opposite of heterologous. To cite the declarations:

(1) **Tracy:**

> It is a "contradiction in terms" to view a homologous gene, sequence, or protein as "heterologous." In the case of the viruses described in Caggana, it is clear to me that the replacement sequence is **not heterologous.**
>
> **(A more detailed quote reads:**
>
> the CB4 nucleic acid sequence (from the -V or -P variant) that replaces the original CB4 sequence in the other virus should not be considered heterologous, *as long as* the replacing sequence is the former sequence's ***homologue*** in the donor genome. The Examiner's extreme interpretation of the definition of "heterologous" used in the application ...makes poor biological sense, in my opinion. This is indeed the case in Caggana when replacing the CB4-P protein 1D with the protein 1D from CB4-V). ... I disagree with the notion that Caggana's "chimeric" ... is "a CB4 virion with

> **heterologous** nucleic acid inserted into an open reading frame that results in fusion to the capsid protein of the virion." It seems to be a contradiction in terms to view a homologous gene, sequence, or protein as "heterologous." In the case of the viruses described in Caggana, it is clear to me that the replacement sequence is **not heterologous.**[)]

(2) **Weiser**

Something that is, in fact, homologous cannot at the same time be heterologous. That situation is completely distinct from this invention - where sequences truly foreign to CB4 viruses are inserted in certain sites to be appropriately expressed so that these recombinant virions can serve as immunogens to evoke immune responses to these non-coxsackievirus peptides.

* * * *

Calling it heterologous is the polar opposite of what I and scientists skilled in this field would call it, the application's definition notwithstanding. Reading the application alone, it is unequivocal to me that the Applicants did not intend to include within their definition of "heterologous polypeptides" other coxsackievirus polypeptides, and certainly not *homologous* CB4 polypeptides as in Caggana.

> (A more detailed quote reads:
>
> Another reason why the "new" CB4 nucleic acid sequence (CB4-V), described in the Caggana paper and replacing the original CB4 sequence in the CB4-P variant, cannot fairly be considered heterologous is because these sequences are, in fact, **homologous:** they encode the same protein with the same biological function, but with one mutated amino acid. Something that is, in fact, homologous cannot at the same time be heterologous. That situation is completely distinct from this invention - where sequences truly foreign to CB4 viruses are inserted in certain sites to be appropriately expressed so that these recombinant virions can serve as immunogens to evoke immune responses to these non-coxsackievirus peptides.
>
> * * * *
>
> The Examiner's interpretation of the definition of "heterologous" used in the application is strained, and not in line with how those in the field view RNA viruses, their nucleic acids, and their proteins, the variation in the sequences of these molecules, and their relationship with one another. It is these relationships that are at the heart of the concepts of 'homologous' and 'heterologous' (because something is homologous or heterologous only to a reference sequence or virus or bacterium or animal species). Thus, I must firmly disagree with the Patent Office's assertion that the virus described in Caggana is
>
> > "a CB4 virion with heterologous nucleic acid inserted into an open reading frame that results in fusion to the capsid protein of the virion".
>
> Rather, it is a CB4 virus in which a segment of a nucleic acid (a viral gene) has been replaced with the **homologous** (albeit non-identical) segment from a very closely related virus of the same taxon. Calling it heterologous is the polar opposite of what I and scientists skilled in

this field would call it, the application's definition notwithstanding. Reading the application alone, it is unequivocal to me that the Applicants did not intend to include within their definition of "heterologous polypeptides" other coxsackievirus polypeptides, and certainly not *homologous* CB4 polypeptides as in Caggana.[)]

(3) **Vande Woude**

I know of no definition of "foreign" or "heterologous," including the definition appearing in the application, that would result in the CB4-P and CB4-V nucleic acid sequences (or their protein products or the viruses which carry them) being called foreign or heterologous to any CB4 virus.

* * * * *

...these two variants cannot be viewed as different viruses. The Patent Offices states that the Caggana reference describes a "heterologous nucleic acid **inserted** into an open reading frame that results in fusion to the capsid protein of the virion." This is backwards: the CB4-P and V sequences are **"homologous,"** the converse of **"heterologous"**. Stated correctly, a portion of the nucleic acid of a CB4 virus "replaces" a *homologous* portion of a nucleic acid of the same length to yield the other variant.

(A more detailed quote reads:

4. The Patent Office's analysis of the paper by Caggana *et al. J Virol. 67*:4797-803 (1993), which was used to reject the claims on the grounds that the claims were anticipated by this paper, is incorrect as I interpret their argument. The rejection asserts that the two viral variants discussed in the paper, CB4-V and CB4-P, are "heterologous." This interpretation is improper because viral variants such as the above two are <u>not</u> foreign or heterologous. Genetically they are two alternative sequences of the same gene -- "alleles" or "allelic variants." I know of no definition of "foreign" or "heterologous," including the definition appearing in the application, that would result in the CB4-P and CB4-V nucleic acid sequences (or their protein products or the viruses which carry them) being called foreign or heterologous to any CB4 virus.

5. As I understand it, the Patent Office has said that it considers the sequences in Caggana *et al.* to be heterologous because "the P1 region of CB4-V was not naturally present in the genome of the CB4-P virus." Whatever this statement means, these two variants cannot be viewed as different viruses. The Patent Offices states that the Caggana reference describes a "heterologous nucleic acid **inserted** into an open reading frame that results in fusion to the capsid protein of the virion." This is backwards: the CB4-P and V sequences are **"homologous,"** the converse of **"heterologous"**. Stated correctly, a portion of the nucleic acid of a CB4 virus "replaces" a *homologous* portion of a nucleic acid of the same length to yield the other variant. "Insertion" of a sequence requires the addition of coding capacity - not present in Caggana, but characteristic of the present invention where foreign sequences are inserted so that a CB4 virion expresses *de novo* a foreign peptide such as an ovalbumin peptide or various HIV peptides.

6. For the reasons cited above, I respectfully disagree with the Patent Office's conclusion that Caggana *et al.* describes "a CB4 virion with *heterologous* nucleic acid *inserted* into an open reading frame that results in fusion to the capsid protein of the virion". That is not an accurate characterization of what is described by this reference.

B. Insertion vs Replacement in Caggana

Furthermore, the Office's insistence on referring to the manipulations performed in Caggana as "insertion" (as intended in the present claims) led each of the Declarants to disagree vigorously.

(1) Tracy (Sec. 6):

...Thus, whether one mutates a nucleotide to change one amino acid, or one excises the coding sequence for 20 contiguous amino acids and puts in its place the mutated coding sequence in which the same nucleotide has been mutated, the outcome is the same. Viruses of the present claims **are also chimeras** -- characterized in this case by the *insertion* of truly heterologous sequences such as ovalbumin or HIV peptides. The process of cloning described by Caggana involved removal of a CB4 sequence, and re-insertion of another related and closely homologous ... CB4 sequence into that space - a 'functional sequence replacement'. As the re-inserted similar sequence was from a very closely related CB4 genome with extremely few differences at the nucleotide and amino acid levels, this represents *replacement* of one sequence with another, nearly identical sequence. It is not insertion, as would be the case if the coding sequence for a non-CB protein such as green fluorescent protein (or an HIV peptide) were inserted into the intact CB genome, making such chimeric virus's nucleic acid molecule longer than that of the parental virus.

(2) Weiser (Sec. 6)

Thus, I must firmly disagree with the Patent Office's assertion that the virus described in Caggana is

> "a CB4 virion with heterologous nucleic acid **INSERTED** into an open reading frame that results in fusion to the capsid protein of the virion".

Rather, it is a CB4 virus in which a segment of a nucleic acid (a viral gene) has been **REPLACED** with the homologous (albeit non-identical) segment from a very closely related virus of the same taxon. *(emphasis -all caps -added).*

(3) **Vande Woude (Sec. 5)**

Stated correctly, a portion of the nucleic acid of a CB4 virus **"REPLACES"** a *homologous* portion of a nucleic acid of the same length to yield the other variant. **"INSERTION"** of a sequence requires the addition of coding capacity - not present in Caggana, but characteristic of the present invention where foreign sequences are inserted so that a CB4 virion expresses *de novo* a foreign peptide ...

C. Fusion

Finally, a point not touched upon directly in the Declarations is the Office's contention that the "heterologous" nucleic acid results in "**FUSION to the capsid protein**". Applicants are somewhat confused with this fusion language, because nothing fused to anything in Caggana. The mutant VP1 protein was expressed. Unless the Office takes the extreme position that every protein is, by definition, a fusion protein (e.g., a 100 amino acid natural protein is a fusion between two 50 residue shorter polypeptides, or between four 25 residue peptides, etc. It should be clear that this can be taken to an absurd point - where the protein is considered a fusion product of 50 tandemly fused amino acid dimers. Absent such an interpretation, the is no "fusion" to a capsid protein in Caggana.

Combining the Declarants' expert opinions on "heterologous" and "insertion vs. replacement," with the above point regarding "fusions," Applicants contend that the Office's conclusion in its § 102 rejection over Caggana, that

> [a]s such, Caggana's chimeric meets the claim limitations of being a CB4 virion with **heterologous** nucleic acid **inserted** into an open reading frame that results in **fusion** to the capsid protein of the virion

is wrong.

- Caggana does not describe a CB4 virion with **heterologous** nucleic acid.
- Caggana does not describe a nucleic acid being **inserted** into an ORF.
- Caggana does not describe a virion that has a heterologous polypeptide **fused to the capsid protein.**

According to the three experts who are clearly suitable representatives of those skilled in the art, the Office simply has Caggana wrong on all counts. The field of RNA viruses of the Picornavirus family is a complicated and specialized area (on top of the underlying knowledge base

of molecular genetics and virology). Hence, it is easy to fall into this trap. Applicants respectfully request the Office to consider carefully these expert opinions, Applicants' other comments, the Caggana reference, the specification and the amended claims, and to withdraw this ground for rejection.

V. Conclusion

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that their amendments and remarks have overcome all the pending grounds for rejection and that all the present claims are in condition for allowance. It would further be proper to rejoin claims 54-72 at this time. Applicants respectfully request early notice of such favorable actions.

Examiner Chen is respectfully requested to contact the undersigned at (202) 496-7845 with any questions or comments if this will assist in understanding this amendment and response.

In the unlikely event that the Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due to **Deposit Account 50-0911**.. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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